Clozapine and risperidone for the treatment of progressive multiple sclerosis (CRISP)

Trial Protocol
Version 14: 29 August 2016
UTN: U1111-1173-2770
ANZCTR: ACTRN12616000178448
# TABLE OF CONTENTS

## LIST OF COMMONLY USED ABBREVIATIONS

General Information

Personnel .......................................................... 5
Participating site(s) ............................................. 5
Funding .............................................................. 5
Ethics ............................................................... 5
Clinical trial registration ..................................... 5
Relevant consultation ......................................... 5

**CRISP TRIAL OVERVIEW**

Hypothesis .......................................................... 6
Background .......................................................... 6
Objectives ............................................................ 7
Primary endpoint .................................................. 7
Secondary endpoints ............................................ 7

**STUDY DESIGN**

Participant selection ............................................ 7
Inclusion criteria ................................................... 7
Exclusion criteria ................................................ 8
Variables being collected ...................................... 9

**STUDY PROCEDURES AND TREATMENT**

Recruitment ........................................................ 10
Consent ............................................................... 11
Randomisation ...................................................... 11
Blinding .............................................................. 11
Information sharing ............................................. 11
Study visits ........................................................ 11
Screening visit ..................................................... 12
Dose-monitoring visits ......................................... 12
Clinical assessment visits ..................................... 12
Weekly monitoring visits ...................................... 12
Progression ........................................................ 12
Study Treatment .................................................. 12
Drug titration ....................................................... 13
Adverse events associated with clozapine ............... 13
Adverse events associated with risperidone ............. 14
Assessment of the acceptability of clozapine and risperidone .......................................................... 15
Ending therapy ..................................................... 15
Withdrawal .......................................................... 15

**SAFETY MONITORING**

Adverse event definitions ...................................... 16
Adverse event and serious adverse event monitoring .......................................................... 17
Minimisation and management of specific major adverse events and risks .......................... 17
Agranulocytosis .................................................... 17
Thrombocytopenia ................................................ 18
Myocarditis/Cardiomyopathy ................................ 18
Hypotension ........................................................ 18
Prolongation of QT Interval .................................... 19
Anticholinergic effects and constipation .................. 19

Fever ................................................................................................................................ 19
Hyperglycaemia and Diabetes Mellitus........................................................................... 20
Weight gain ...................................................................................................................... 20
Thromboembolism ......................................................................................................... 20
Cerebrovascular .............................................................................................................. 20
Seizures ............................................................................................................................ 20
Tardive Dyskinesia ......................................................................................................... 21
Neuroleptic Malignant Syndrome ................................................................................ 21
Dysphagia ....................................................................................................................... 21
Hyperprolactinaemia ..................................................................................................... 21
Liver disease .................................................................................................................. 22
Pregnancy ....................................................................................................................... 22
Lactation .......................................................................................................................... 22
Effects on ability to drive and use machines ................................................................... 22
Trial Safety Review ......................................................................................................... 22
PATIENT COMPENSATION ............................................................................................. 23
DATA MANAGEMENT .................................................................................................... 23
Case report forms ............................................................................................................ 23
Confidentiality and storage ............................................................................................ 23
MANAGEMENT OF STUDY MEDICATIONS ................................................................. 23
  Medicine checking and storage ................................................................................... 23
  Supply of study medicines to participants .................................................................... 24
  Protocol for administering suspension ....................................................................... 24
  Disposal of used and unused study treatments .......................................................... 24
STATISTICS .................................................................................................................... 24
  Sample size .................................................................................................................. 24
  Data analysis ............................................................................................................... 24
PROJECT TIMELINE ...................................................................................................... 24
FUTURE RESEARCH ..................................................................................................... 25
APPENDIX 1: SCHEDULE OF VISITS FOR TRIAL PARTICIPANTS ......................... 28
LIST OF COMMONLY USED ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse events</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CCDHB</td>
<td>Capital and coast district health board</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>EAE</td>
<td>Experimental autoimmune encephalomyelitis</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDSS</td>
<td>Expanded disability status score</td>
</tr>
<tr>
<td>FBC</td>
<td>Full blood count</td>
</tr>
<tr>
<td>FSS</td>
<td>Fatigue severity scale</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>MSFC</td>
<td>Multiple sclerosis functional composite</td>
</tr>
<tr>
<td>NHI</td>
<td>National health index</td>
</tr>
<tr>
<td>NMS</td>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>PMS</td>
<td>Progressive multiple sclerosis</td>
</tr>
<tr>
<td>RRMS</td>
<td>Relapsing-remitting multiple sclerosis</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>TSQM</td>
<td>Treatment satisfaction questionnaire for medication</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood count</td>
</tr>
</tbody>
</table>
GENERAL INFORMATION

Personnel

Principal Investigator
Prof Anne La Flamme
School of Biological Sciences, Victoria University of Wellington
Head, Multiple sclerosis Research Programme, Malaghan Institute of Medical Research
anne.laflamme@vuw.ac.nz
+64-4-463-6093

Principal Clinical Investigator and Treating Neurologist
Dr David Abernethy
Head of Neurology, Wellington Regional Hospital
Capital and Coast District Health Board
David.Abernethy@ccdhb.org.nz
027 241 8396 (mobile)

Research Nurse
Liz Goode
Wellington Regional Hospital
Capital and Coast District Health Board
Liz.Goode@ccdhb.org.nz
(04) 806-0078 (office) / 021 258 2075 (mobile)

Participating site(s)
Neurology Department and Clinical Trials Unit, Wellington Regional Hospital

Funding
Funding is being sought from a variety of organizations.

Ethics
Approval has been granted from the Central Health and Disability Ethics Committee (15/CEN/216) and SCOTT (15/SCOTT/177).

Clinical trial registration
This clinical trial is registered with www.anzctr.org.au (ACTRN12616000178448).

Relevant consultation
This project was discussed with the Research Advisory Group – Maori (RAG-M) through Maori Health Development Group, Capital and Coast District Health Board.

CRISP TRIAL OVERVIEW
The CRISP study is a blinded, placebo-controlled clinical trial of clozapine and risperidone administration in progressive multiple sclerosis (PMS) patients. The study is based upon preclinical data from two mouse models of MS (multiple sclerosis; experimental allergic encephalitis and the cuprizone model of demyelination), showing clozapine and risperidone reduce immune-mediated damage and disease. The aim of the CRISP trial is to assess the safety and acceptability of clozapine and risperidone in PMS patients.
Thirty-six patients with PMS will be recruited through the Neurology Department at Wellington Hospital with the expectation of 33 completing the trial. Baseline clinical and laboratory investigations will be taken and patients (n = 12/group) will receive oral clozapine titrated to a final dose of 150 mg/day (1, 2), risperidone titrated to a final dose of 3.5 mg/day, or placebo. Over the course of the 6 month participation in the trial, patients will have regular clinical review and blood sampling. The primary outcome measure is the safety and tolerability of clozapine and risperidone treatment. Secondary outcome measures include disability progression.

**Hypothesis**
We hypothesise that 1) treatment with low dose clozapine or an average daily dose of risperidone in patients with PMS will be well tolerated and 2) adverse effects in this population will be similar to those documented in patients with schizophrenia.

**Background**
MS affects 1 in 1400 New Zealanders, with approximately 34% of MS patients suffering from moderate to severe disability (3). Eighty-five percent of all patients with MS have relapsing-remitting MS (RRMS), which is characterized by a focal neurological deficit called a relapse, followed by full or partial resolution or remission (4). Forty-five percent of these patients will eventually develop secondary PMS in which neurological disability worsens with time (3).

There is no cure for MS and current FDA approved disease modifying treatments are limited in terms of efficacy, mode of administration, availability due to cost, and concerns regarding potentially fatal side effects (5, 6). Therefore, there is a need for more effective and more easily tolerated treatments to be developed as well as treatments that target PMS for which there are currently no effective, long-term treatments.

The event that initiates MS is unknown but it is clear that once established, the disease is mediated by immune cells damaging the myelin sheaths that surround and insulate neuronal axons (7). The pathogenic role of the immune system in MS is highlighted by the ability of immunomodulatory or immunosuppressive agents to reduce disease. Indeed, all current disease-modifying therapies work by targeting the immune system (6).

Clozapine and risperidone are atypical anti-psychotic agents originally developed in 1959 (8) and 1992, respectively, and are used to treat several mental illnesses including schizophrenia. Clinical trials for the treatment of schizophrenia demonstrated efficacy in the 1960s and 1970s; however, use of clozapine in clinical practice was suspended in the 1970s due to fatalities resulting from agranulocytosis, which occurs in 0.7% of the population. It was reintroduced into clinical practice in the 1990s after superior efficacy in the treatment of schizophrenia was again demonstrated, but with strict protocols for its use (9, 10). Recent studies have identified genetic markers of susceptibility to clozapine-induced agranulocytosis (e.g. HLA-DQB1-*0201 and HLA-B38) providing hope that patients with susceptibility to agranulocytosis can be identified (11-13).

Clozapine and risperidone are potent dopamine type 2 (D2) and serotonin type 2 (5HT2) receptor antagonists (8, 14). Recent studies indicate that these agents have anti-inflammatory actions on microglia, central nervous system (CNS)-resident macrophages (15). Experiments by O’Sullivan et al. evaluating the effect of clozapine and risperidone treatment in the mouse...
model of MS, experimental autoimmune encephalomyelitis (EAE), show a dose-dependent reduction in the severity of disease and that clozapine treatment promotes disease resolution (16). There is an approximate 50% reduction in lesion formation in EAE mice treated with clozapine or risperidone compared to untreated EAE mice, and this reduction in disease is similar to the optimal dose of glatiramer acetate (500 μg) in this model (17).

The CRISP trial outlined in this protocol investigates and compares clozapine and risperidone treatment in patients with PMS. This is the first trial of clozapine or risperidone in humans to treat MS disease although there have been several case reports describing the successful use of risperidone in MS patients to treat MS-associated psychosis (18, 19). The side-effect profiles of both clozapine and risperidone are well known when used to treat patients with schizophrenia, and thus, the primary aim of this study is to determine if doses of 100-150 mg of clozapine and 2-3.5 mg of risperidone are safe and well tolerated in patients with PMS.

**Objectives**

**Primary endpoint**

The primary end points of this trial are the safety and acceptability of clozapine and risperidone in a PMS population. Safety will be assessed by calculating the incidence rate of adverse events (AE) and serious adverse events (SAE). The incidence of AE and suspected study drug-related AE will be summarized as the frequency count as well as the percentage of patients with AE. The incidence of SAE and AE leading to premature discontinuation of study drug will be summarized. Acceptability will be assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM-9) to psychometrically evaluate the patients' satisfaction with clozapine or risperidone, compared to a placebo group. The TSQM-9 is a sound and valid measure of the major dimensions of patients' satisfaction with medication (20).

**Secondary endpoints**

We will also compare the potential efficacy of clozapine and risperidone in PMS using clinical measures. Clinical measures will include the MS functional composite (MSFC), the expanded disability status score (EDSS), and the fatigue severity scale (FSS).

**STUDY DESIGN**

This study will be a blinded, placebo-controlled trial of clozapine and risperidone treatment in PMS patients. A total of 36 patients will be recruited and split into three treatment groups. Thirty-six patients (n = 12/group) will be recruited according to strict inclusion and exclusion criteria, and titrated to receive clozapine at a final dose of 150 mg/day, risperidone at 3.5 mg/day, or placebo for six months (1, 2). These recruitment numbers allow for the drop out of 1 participant per group.

**Participant selection**

To be eligible for inclusion into this trial, the subjects must fulfil all of the following criteria:

**Inclusion criteria**

1. Progressive multiple sclerosis with the continuous worsening of neurological impairment over at least 6 months
2. Aged 18 years to 70 years
3. An EDSS at baseline of 3.5 to 7.0
4. Willing and able to participate in the trial and provide written, informed consent
Exclusion criteria
1. Relapsing-remitting MS
2. Pregnant or lactating women
3. Patients unable to undergo regular blood tests or MRI scans
4. Patients with contraindications to clozapine or risperidone
5. Known hypersensitivity to clozapine, risperidone or to any of the excipients thereof
6. Reported past intolerance to clozapine or risperidone
7. Postural hypotension, defined as a reduction in systolic blood pressure (BP) of 20 mmHg within 2 – 5 minutes of standing up
8. Dysphagia
9. Current diagnosis of substance abuse or history of alcohol or drug abuse in the past 3 months
10. Concomitant disease likely to interfere with the trial medication (e.g. capable of altering absorption, metabolism or elimination of the trial drug)
11. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy)
12. Impaired bone marrow function
13. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions
14. History of circulatory collapse and/or CNS depression of any cause
15. Moderate or severe renal or cardiac disorders (e.g. myocarditis)
16. Hepatic impairment; active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure
17. Paralytic ileus
18. History of cardiovascular disease
19. Elevated glycosylated haemoglobin levels (HbA1c; ≥ 41mmol/mol)
20. Hyperthyroidism
21. Serious medical co-morbid illness or any other disease or condition which, in the opinion of the investigator, means that it would not be in the patient’s best interests to participate in the study
22. A white blood cell (WBC) and differential blood count taken within 10 days of starting treatment shows a WBC count of < 3500/mm$^3$ and absolute neutrophil count (ANC) of < 2000/mm$^3$
23. An abnormal platelet count taken within 10 days of starting treatment
24. Concomitant use of medications known to affect clozapine treatment:
   a. Fluvoxamine, ciprofloxacin, or enoxacin
   b. Oral contraceptives
   c. Cimetidine, escitalopram, erythromycin, paroxetine, bupropion, fluoxetine, quinidine, duloxetine, terbinafine, or sertraline
25. Concomitant use of medications known to reduce the effectiveness of clozapine treatment, including phenytoin, carbamazepine, St John’s wort, rifampin
26. Patients taking drugs that increase the risk of agranulocytosis, including carbamazepine, phenylbutazone, azapropanone, co-trimoxazole, penicillamine, cytotoxic agents, sulphonamide antibiotics, or chloramphenicol
27. Patients taking medications that prolong the QT interval or inhibit clozapine metabolism, including ziprasidone, iloperidone, chlorpromazine, thioridazine, mesoridazine, droperidol, pimozide, erythromycin, gatifloxacin, moxifloxacin, sparfloxacin, quinidine, procainamide, amiodarone, sotalol, pantamidine, levomethadyl acetate, methadone, halofantrine, melfoquine, dolaseton mesylate, probucol, or tacrolimus.
28. Patients taking other medications that may potentiate the side effects of treatment with atypical antipsychotics, including frusemide or anti-cholinesterase treatment
29. Treatment with cyclophosphamide or mitoxantrone within 12 months; systemic corticosteroid therapy within 30 days; treatment with interferon beta, glatiramer acetate, natalizumab, fingolimod, dimethyl fumerate, plasmapheresis, or intravenous immunoglobulin within 60 days

Variables being collected
1. Clinical
   a. Baseline data:
      - Name
      - National health index (NHI)
      - Date of birth
      - Sex
      - Ethnicity
      - Height and weight, calculate body mass index
      - Smoking status
      - Currently prescribed/used medications
      - Details of any other chronic illnesses/diseases
      - Previous disease monitoring therapies/steroids
      - Time since first relapse
      - Relapses in previous 2 years
   b. Clinical assessments (0, 3 and 6 months):
      - EDSS – Expanded disability status score (30 minutes)
      - MSFC – Multiple sclerosis functional composite (1 hour)
      - FSS – Fatigue severity scale (30 minutes)
      - TSQM-9 – Treatment Satisfaction Questionnaire for Medication (3 and 6 months only; 30 minutes)
      - MRI – Magnetic resonance imaging (0 and 6 months only)
   c. Clinical assessment of adverse events (Weekly consult with Research Nurse):
      - AE/SAE – adverse events and serious adverse events collected and reviewed by Treating Neurologist
   d. Clinical assessment of adverse events (Baseline and at 3 and 6 months):
      - Temperature
      - Heart rate (HR)
      - Lying and standing BP
      - Weight
      - Electrocardiogram (ECG) with QTc
      - Echocardiogram (baseline only)

2. Laboratory
   a. Clinical visit haematology (measured at 0, 3 and 6 months)
      - The volume of blood required is:
         - 2 x 4 ml EDTA
         - 8.5 ml SST
         - 1 x 8 ml CPT with heparin
         - 1 x 5 ml CytoChex tube
      - Liver and renal function:
         - ALT – Alanine aminotransferase/Transaminase
• ALP – Alkaline phosphatase
• GGT – Gamma glutamyltransferase
• BILI – Total bilirubin
• ALBU – Serum albumin
• SP – Total serum protein
• CREAT – Serum creatinine
• CPK – Creatine phosphokinase

Other:
• FBC – Full blood count
• CRP – C reactive protein
• HbA1c – Glycosylated haemoglobin
• PRL – Prolactin
• TNT – Troponin T

b. Monitoring haematology
- Weekly from weeks 1 – 4:
  - FBC – Full blood count
  - TNT – Troponin T
  - CRP – C reactive protein
- Weekly from weeks 5 – 18, 4-weekly thereafter:
  - FBC – Full blood count

3. Immunological
- Blood, serum, and isolated peripheral blood mononuclear cells from samples collected at baseline and 3 and 6 months (CPT tubes) will be analysed and stored at Victoria University to assess the effect of treatment on immunological parameters during the study period. These studies will include immune phenotyping by flow cytometry and immune cell responses.

**STUDY PROCEDURES AND TREATMENT**

**Recruitment**
Patients with PMS will be identified on the neurology ward, in neurology outpatient clinics, and through a review of existing databases. Cases will also be identified through referral by Wellington Hospital neurologists. Patients will be identified as they attend the neurology department and will be asked if they wish to be involved in this study. Those identified through personal recollection, databases or review of discharge diagnostic coding will be contacted by telephone or mail and provided with an information sheet. Participants will be approached by their neurologist, the principal investigator or one of the sub-investigators, or an MS nurse specialist. In addition, awareness about the study will be created through advertising on the Malaghan Institute of Medical Research website and discussion with media (via radio, television, and newspaper articles). Potential study participants who initiate contact with the study investigators will be provided with an information sheet and followed up with by a study investigator.
Consent
Potential study subjects will be provided with an information sheet and given as much time as they require to read it. The Treating Neurologist will then explain the study to the participant and answer any questions they may have. A member of the research team will obtain formal written consent. The explanation of the study and consent process will be conducted at Wellington Hospital.

Randomisation
A random allocation sequence using a block size of 9 with no stratification will be generated using a third party online randomisation sequence generator (www.randomization.com) to allocate a study medication to each participant study number in sequence. A research nurse who is not otherwise associated with the CRISP trial will generate the randomisation sequence and will provide sealed individual participant randomisation envelopes. An envelope for a specific study participant can be opened if the site staff needs to know which treatment the participant has been receiving. These envelopes will be kept in a secure location that can be accessed by the Treating Neurologist in an emergency. Finally, the randomisation schedule will be kept concealed in a locked filing cabinet in the Clinical Trials Unit for the duration of the study.

Blinding
The Treating Neurologist, Assessing Neurologist, and the participants will be blinded as to the treatment allocation. However, in accordance with the safety monitoring procedures of the study, the Treating Neurologist may unblind a participant’s treatment allocation if required for safety reasons. Unblinded site staff are the pharmacy personnel and the Research Nurse.

Information sharing
The study medications have a wide range of potential side effects and contraindications; therefore, it is important that all health practitioners involved in the care of the study patient are aware of their participation in the CRISP trial. Participants will be told when seeking treatment to inform all medical professionals that they may be taking a study medication. In addition, the Treating Neurologist will add a note to the patient’s hospital records to indicate that the patient may be receiving either clozapine or risperidone and list the most serious adverse events that could result from use of these medications (agranulocytosis, myocarditis or cardiomyopathy, and neuroleptic malignant syndrome (NMS)).

Participants will also be asked for the contact details of their general practitioner during the consent process, and the general practitioner will be notified of the patient’s enrolment in the study by letter. In the event that a study participant experiences an adverse event that requires treatment and/or monitoring by their general practitioner, the relevant patient notes will be provided by the Treating Neurologist. Lastly, participants will be supplied with a wallet card explaining their study participation and the contact details for the study investigators.

Study visits
The study subjects will participate in visits for screening and baseline data collection, dose-monitoring, clinical assessment after 3 and 6 months of treatment, and weekly haematology testing, as described in the following sections. The full schedule of visits and procedures is outlined in Appendix 1.
**Screening visit**
At screening patients will be evaluated by the Treating Neurologist (Dr Abernethy). The Treating Neurologist will talk the patient through the details of the study and obtain informed consent. Baseline details will be collected, and inclusion and exclusion criteria will be considered. The Assessing Neurologist will perform the EDSS, FSS, and the MSFC, and the Research Nurse will perform the ECG and coordinate the echocardiogram. At completion of the screening data collection, the Treating Neurologist will ensure patients meet inclusion criteria and provide informed consent. Participants eligible for participation who consent to being in the study will undergo baseline blood tests.

**Dose-monitoring visits**
Participants eligible to receive the study medicines will be randomized to receive clozapine, risperidone, or placebo and the first five doses will be administered during dose-monitoring visits. These visits will be attended at Wellington Hospital on five consecutive days beginning with the Monday of the first week of study participation. An MRI will be performed prior to administration of the first dose of medication. Due to the risk of hypotension, patients will be encouraged to remain in a supine position and will be observed for a period of four hours following each of these doses. After the first and second doses, the Research Nurse will observe the patient continuously during this period and measure temperature, pulse, and the standing and sitting blood pressures hourly. Subsequent visits will not require continuous monitoring, but will involve taking vital measurements 2 and 4 hours after receiving the medicine. Based on the participant response to the medication, the Research Nurse and/or Treating Neurologist may schedule further dose-monitoring visits during the second week of the initial titration period, at their discretion. Refer to Appendix 2 for a comprehensive description of the dose-monitoring visits.

**Clinical assessment visits**
After 3 and 6 months of treatment, patients will be seen and evaluated by the Treating Neurologist (clinical assessment), Assessing Neurologist (EDSS, FSS, MSFC, TSQM-9), and Research Nurse (ECG). At 6 months, an MRI will also be performed and will be coordinated by the Research Nurse.

**Weekly monitoring visits**
The participants will have FBCs monitored weekly for the first 18 weeks of the study, and approximately 4 weekly thereafter. The monitoring will be done by the Research Nurse under the guidance of the Treating Neurologist, and these visits will include a verbal consultation with the Research Nurse to monitor the occurrence of AE and SAE. It is required that the study participant visit Wellington Hospital and meet with the Research Nurse in person for these visits at least once per fortnight. If preferable, the participants may opt to have the haematology performed at their local Southern Community Laboratories site and complete a verbal consultation with the Research Nurse over the phone for the weekly monitoring in between the compulsory fortnightly visits to Wellington Hospital.

**Progression**
Participants will be evaluated at an unscheduled visit if a clinically significant change in their condition has occurred. In these cases, the participant will be evaluated and an EDSS performed by the Treating Neurologist.

**Study Treatment**
Drug titration
The active medication will be a clozapine suspension, risperidone tablets, or a placebo matched to the active medication and will be provided by Douglas Pharmaceuticals Ltd. Food intake does not affect the absorption of clozapine or risperidone; however, smoking and caffeine may alter the efficacy of clozapine treatment. Patients will be observed in the clinic for a period of 4 hours after taking their first five consecutive daily doses, with the potential for a second week of monitoring if deemed necessary by the Research Nurse. Patients will be supplied with a Study Medication Diary detailing when and how much of the study medicines to take, and the importance of contacting the Research Nurse if they begin taking any other medicines, experience any adverse events, or substantially deviate from their usual smoking habits and/or caffeine intake. Those allocated to the placebo group will take the placebo in an identical manner as the matched active medication including a titration schedule that matches the active medication.

Participants will be started on clozapine at a dose of 5 mg/day and titrated over 2 weeks to an interim daily dose of 100 mg/day for 2.5 months. The dose will be held at the same level across the weekends. After the 3-month clinical visit, the dose of clozapine will then be further titrated over 2 weeks to a final dose of 150 mg/day. This titration schedule is based upon the Adult Clozapine Titration Chart (1).

Participants will be started on risperidone at a dose of 0.5 mg/day and titrated over 2 weeks to an interim daily dose of 2.0 mg/day for 2.5 months. Following the 3 month clinical visit, the dose of risperidone will then be titrated over 2 weeks to a final dose of 3.5 mg/day based upon Luchins et al. (22), who recommend a slow titration.

The titration schedule may be altered to suit individual responses. For instance, if it is felt that a participant would benefit from a more gradual increase in medication dose, the schedule can be amended accordingly. Because the study medicines may have sedative effects, it is recommended that either the majority or entire daily dose is taken at night during the initial titration period. When taking the maintenance dose from day 15 onwards, patients may choose which time of day they take the medication in order to suit their personal needs and situation.

Table 1: Schedule of clozapine and risperidone titration in mg/day

<table>
<thead>
<tr>
<th>Study Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15 - 91</th>
<th>92 - 98</th>
<th>99 - 105</th>
<th>106 - 180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>M</td>
<td>T</td>
<td>W</td>
<td>Th</td>
<td>F</td>
<td>Sat</td>
<td>Sun</td>
<td>M</td>
<td>T</td>
<td>W</td>
<td>Th</td>
<td>F</td>
<td>Sat</td>
<td>Sun</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>25</td>
<td>45</td>
<td>45</td>
<td>60</td>
<td>60</td>
<td>85</td>
<td>85</td>
<td>100</td>
<td>120</td>
<td>135</td>
<td>150</td>
</tr>
<tr>
<td>Total:</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>50</td>
<td>70</td>
<td>70</td>
<td>85</td>
<td>85</td>
<td>100</td>
<td>120</td>
<td>145</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>AM</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse events associated with clozapine
Clozapine has only weak dopamine receptor-blocking activity at D1, D2, D3 and D5

receptors, but shows high potency for the D4 receptor, in addition to potent anti-alpha-adrenergic, anti-cholinergic, anti-histaminic, and arousal reaction-inhibiting effects (8, 23). Clozapine has also been shown to possess anti-serotonergic properties (8).

Clozapine is unique in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia (10, 23). Furthermore, parkinsonian-like AE and akathisia are rare. In contrast to classical antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding AE such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence (8). The most common AE occurring in more than 1 in 10 patients are weight gain, drowsiness, sedation, dizziness, tachycardia, constipation, and hypersalivation (10, 23, 24).

Clozapine is indicated in patients with treatment-resistant schizophrenia (23), where dosing typically begins at 12.5 mg once or twice a day (1, 2). The daily dose is then increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks (1, 2). To enhance the acceptability of clozapine, the titration in the present study will be done slowly over a period of 2 weeks beginning at a daily dose of 5 mg/day and gradually increasing until a final daily dose of 100 or 150 mg/day is achieved.

Many of the AE caused by clozapine occur in a dose-dependent manner, and the threshold at which these AE appear is close to 100 mg/day (10). The average daily dose of clozapine in schizophrenic patients is 300-400 mg, which is markedly higher than the final daily dose of 150 mg proposed in our study (2).

Adverse events associated with risperidone
Risperidone has strong dopamine receptor-blocking activity at D2, D3 and D4 receptors, which are all type 2 dopamine receptors. In addition, risperidone has potent anti-alpha-adrenergic and anti-serotonergic properties (8).

Risperidone’s strong D2 receptor antagonism has been associated with extrapyramidal AE such as acute dystonia and tardive dyskinesia (8, 25). In contrast to clozapine, risperidone treatment leads to hyperprolactinemia, which is associated with AE such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence (8, 26). The most AE occurring in more than 1 in 10 patients are weight gain, dizziness, vomiting, dry mouth, nausea, anxiety, constipation, and hypersalivation (8, 25).

Risperidone is used to treat schizophrenia, mania in bi-polar disorder, the behavioural and psychological symptoms of dementia, and autism in children (25). Dosing typically begins at 2.0 mg once a day to treat schizophrenia and 0.5 mg/day for treatment in the elderly (25). The daily dose is then increased slowly in increments of 0.5 mg/day in order to achieve a dose level of between 4-6 mg/day within 2 weeks (26, 29). Doses above 10 mg day have not been found to provide any extra benefit compared to lower doses and doses above 16 mg/day are not recommended (25).

To enhance the acceptability of risperidone, the titration in the present study will be done slowly as recommended (27) over a period of 2 weeks, beginning at a daily dose of 0.5 mg/day and gradually increasing until a final daily dose of 2 or 3.5 mg is achieved. The average daily dose of risperidone is 4-6 mg/day compared to our study, which proposes a final daily dose of 3.5 mg/day (25).
Assessment of the acceptability of clozapine and risperidone
At the 3 and 6-month clinical visits, the acceptability of clozapine and risperidone, compared to the placebo, will be assessed by a modified TSQM questionnaire containing 9 questions (TSQM-9) in 3 domains (effectiveness, convenience, and global satisfaction) as follows (20):

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
4. How easy or difficult is it to use the medication in its current form?
5. How easy or difficult is it to plan when you will use the medication each time?
6. How convenient or inconvenient is it to take the medication as instructed?
7. Overall, how confident are you that taking this medication is a good thing for you?
8. How certain are you that the good things about your medication outweigh the bad things?
9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

Ending therapy
At the conclusion of the study, or if patients opt to withdraw from the study, patients will be instructed to gradually reduce the dose of the treatment over a period of 12 days, as outlined in Table 2.

Table 2: Schedule of clozapine and risperidone dose reduction at study completion in mg/day

<table>
<thead>
<tr>
<th>Study Day:</th>
<th>181 &amp; 182</th>
<th>183 &amp; 184</th>
<th>185 &amp; 186</th>
<th>187 &amp; 188</th>
<th>189 &amp; 190</th>
<th>191 &amp; 192</th>
<th>193</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>25</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PM</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>50</td>
<td>25</td>
<td>12.5</td>
<td>-</td>
</tr>
<tr>
<td>Total:</td>
<td>125</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>12.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Day:</th>
<th>181 &amp; 182</th>
<th>183 &amp; 184</th>
<th>185 &amp; 186</th>
<th>187 &amp; 188</th>
<th>189 &amp; 190</th>
<th>191 &amp; 192</th>
<th>193</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PM</td>
<td>3.0</td>
<td>2.5</td>
<td>2.0</td>
<td>1.5</td>
<td>1.0</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>Total:</td>
<td>3.0</td>
<td>2.5</td>
<td>2.0</td>
<td>1.5</td>
<td>1.0</td>
<td>0.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Withdrawal
The patient may withdraw from the study at any time, for any reason. The Treating Neurologist may also withdraw the patient from the study if it is felt to be in the patient’s best interests for reasons including, but not limited to, those specified in the strategies for minimising and managing adverse events of treatment. The reason for withdrawal will be recorded by the Treating Neurologist on the case report form (CRF). Data collected from participants that are withdrawn from the study will be included in the primary endpoint analysis (safety and acceptability of treatment), but not in the secondary endpoint analysis (potential efficacy of treatment).

It will be recommended that study participants withdrawing before study completion follow the gradual dose reduction schedule outlined for patients finishing treatment. In the event that...
treatment must be terminated abruptly due to AE, patients will be provided with information about the potential adverse events of immediately ceasing treatment and instructed to contact the Treating Neurologist or Research Nurse if they have any concerns. In particular, clozapine has anti-cholinergic effects; therefore sudden withdrawal of treatment may result in symptoms of cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhoea. If patients are required to abruptly terminate clozapine treatment, the Treating Neurologist may prescribe a single dose of the anti-cholinergic medicine, cogentin. Further appointments with the clinical trial staff or the patients’ healthcare practitioners will be scheduled to assess and manage any AE requiring, or resulting from, withdrawal of treatment, until the effects resolve.

SAFETY MONITORING

Adverse event definitions
AE are defined as any untoward medical occurrence in a study subject temporally associated with participation in the trial and the administration of study medication, whether or not considered related to the medicine. It is recognised that the patient population participating in this study may experience a number of aberrations in laboratory results, signs, and symptoms due to the nature of the underlying disease, PMS. These events will not necessarily constitute an AE unless they require significant intervention or are considered to be of concern in the Treating Neurologist’s clinical judgement.

A serious adverse event (SAE) is an AE (at any dose of study drug) that:
- results in death
- is life-threatening, i.e., the participant was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death)
- results in persistent or significant disability/incapacity
- requires in-participant hospitalization or prolongs existing hospitalization
- is a congenital anomaly/birth defect
- is another medically significant event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

Expedited Reporting:
All SAEs that result in the breaking of the study code must be reported to Medsafe within 72 hours of the site realising that the event has occurred and as soon as possible to the ethics committee. In addition all Serious Adverse Events that result in hospitalization or death must be reported to the ethics committee as soon as possible.

Routine Reporting:
All other SAEs should be presented in the 6-monthly report to the regulatory authority and the annual report to the ethics committee.
**Adverse event and serious adverse event monitoring**
The incidence of side effects and/or AE will be monitored on a weekly basis during weeks 1 – 18, and 4 weekly thereafter, by consultation with the Research Nurse. During these consultations, patients will be screened for unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia or palpitations.

Specifically, the Research Nurse will ask about and assess:
1. any adverse effects from the study medication
2. drowsiness, sedation, dizziness, tachycardia, constipation, hypersalivation
3. unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia or palpitations
4. symptoms of postural dizziness
5. bowel habits
6. symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia
7. symptoms of hyperprolactinaemia including irregular menses, galactorrhoea, decreased libido, impotence

The occurrence of any such signs or symptoms will be referred to the Treating Neurologist for further evaluation. Additionally, FBC will be monitored at these appointments for the first 18 weeks, and 4 weekly thereafter until 4 weeks after discontinuation of treatment.

**Minimisation and management of specific major adverse events and risks**
The weekly visits/phone calls with the Research Nurse for the first 18 weeks of the study are designed to minimise and manage a number of potential side effects of clozapine and risperidone treatment that have been previously identified. The Treating Neurologist will assess patients experiencing any such signs or symptoms and determine the necessary course of action in accordance with the following specific strategies. If necessary for safety reasons, the Treating Neurologist may unblind a participant’s treatment allocation to aid in the management of possible adverse events.

**Agranulocytosis**
- **Risk:** The risk of granulocytopenia in the general population taking clozapine is 3% and for agranulocytosis the risk is 0.7% (23). The frequency of agranulocytosis with risperidone is less than 1 in 10,000 (25).
- **Action to prevent:** FBCs within 10 days of starting treatment. Treatment is restricted to patients with a WBC count $\geq 3500$/$\text{mm}^3$ (3.5 $\times$ 10^9/L) and an ANC $\geq 2000$/$\text{mm}^3$ (2.0 $\times$ 10^9/L), and within standardized normal limits. Only patients with normal leukocyte and neutrophil counts (WBC $\geq 3500$/$\text{mm}^3$ (3.5 $\times$ 10^9/L) and ANC $\geq 2000$/$\text{mm}^3$ (2.0 $\times$ 10^9/L)) will be included.
- **Action within trial to minimize risk:** Agranulocytosis and granulocytopenia are reversible if clozapine is withdrawn promptly in the majority of cases. Therefore, FBC will be monitored weekly for 18 weeks, and thereafter at least every four weeks throughout treatment. Additionally, FBC will be monitored 4 weeks after complete discontinuation of treatment. At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. A differential blood count must be performed immediately if any symptoms or signs of an infection occur. The clinical investigator will be responsible for monitoring the FBC.
Action taken if event occurs: Changes in WBC counts will be managed using the guidelines recommended by Medsafe (23):

- If the WBC count is between 3.0 and 3.5 x 10^9/L and/or the ANC is between 1.5 and 2.0 x 10^9/L, blood tests will be required at least twice a week until the WBC and ANC stabilize within this range, or higher than this range.
- If a patient has a WBC < 3.0 x 10^9/L and/or ANC < 1.5 x 10^9/L, clozapine treatment will be interrupted and blood tests will be taken on the two following days. If the results are below these threshold values for either of the subsequent tests, clozapine treatment will be discontinued and patients will receive daily FBCs until the neutrophil count is > 1.5 x 10^9/L.

Thrombocytopenia

Risk: The frequency of thrombocytopenia in patients receiving clozapine or risperidone treatment is less than 1 in 10,000 (23, 25).

Action to prevent: FBCs within 10 days of starting treatment. Only patients with normal platelet count will be included in the trial.

Action within trial to minimize risk: Platelet count will be monitored weekly for 18 weeks, and thereafter at least every four weeks throughout treatment and for 4 weeks after discontinuation of the treatment. The Research Nurse will be responsible for monitoring the full blood counts.

Action taken if event occurs: Treatment will be discontinued if the platelet count falls below 150,000/mm^3 (150 x 10^9/L).

Myocarditis/Cardiomyopathy

Risk: The reported global incidence of myocarditis is rare (<0.1%) during the first month of clozapine therapy and very rare (<0.01%) thereafter. Some cases of myocarditis have been reported to be fatal (incidence approximately 0.2 cases/100,000 patient years) and have occurred in patients taking doses of 12.5 mg and above. Cardiomyopathy usually occurs later in clozapine treatment than myocarditis (23).

Action to prevent: Patients with known cardiac disease will be excluded from the trial. A screening ECG and echocardiogram will be taken prior to patients being enrolled in the trial (29). Clozapine treatment will be slowly titrated over the first two-week period beginning at 5 mg once daily.

Action within trial to minimize risk: Patients will be monitored by the Research Nurse at Wellington Hospital for 4 hours following each of the first five doses of study medication, and troponin and CRP levels will be measured during the screening visit and then weekly for the first 4 weeks of treatment (29). The nurse will screen patients for unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia or palpitations during weekly monitoring visits. The occurrence of these symptoms will necessitate an urgent diagnostic evaluation for myocarditis.

Action taken if event occurs: If the diagnosis of myocarditis or cardiomyopathy is suspected, clozapine will be discontinued. Cardiology assessment will be undertaken to assess for cardiac disease and an ECG referred for cardiological assessment.

Hypotension

Risk: Orthostatic hypotension, with or without syncope, can occur during clozapine treatment (23).

Action to prevent: Patients participating in the trial will have lying and standing blood pressure recordings at baseline. Those with postural hypotension at baseline will be
excluded from the trial. Patients will be slowly titrated onto clozapine over two weeks (23).

- Action within trial to minimize risk: The Research Nurse will monitor patients at Wellington Hospital for 4 hours after taking each of the first five doses of medication. Patients participating in the trial will be asked about symptoms of postural dizziness during the weekly monitoring visits for the first two weeks of the study, then monthly throughout the trial. They will have lying and standing blood pressure recordings at 3 and 6 months.
- Action taken if event occurs: If hypotension persists throughout the first week of commencing the study treatment, a second week of in-home monitoring will be arranged.

Prolongation of QT Interval
- Risk: Prolongation of the QT interval has been observed with atypical antipsychotic drug use (23, 25).
- Action to prevent: Patients with known cardiovascular disease, a family history of QT prolongation, or prolonged QT on ECG at baseline will be excluded from the trial.
- Action within trial to minimize risk: A repeat ECG at 3 and 6 months will be performed to ensure QT is within the normal range.
- Action taken if event occurs: If an ECG shows QT prolongation as greater than 500 ms (using the correct correction formula) treatment will be discontinued (29).

Anticholinergic effects and constipation
- Risk: Clozapine exerts anticholinergic activity, which may produce AE throughout the body. Clozapine treatment has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation (frequency ≥1/10) to intestinal obstruction, faecal impaction, and paralytic ileus (all at frequencies ≤1/10,000). These effects are dose-related and on rare occasions have proved fatal (28). Intestinal obstruction with risperidone treatment is very rare (≤1/10,000; 25).
- Action to prevent: Patients with paralytic ileus will be excluded from participating in the trial.
- Action within trial to minimize risk: Participants in the study will be questioned about their bowel habits during weekly monitoring visits with the Research Nurse.
- Action taken if event occurs: In milder cases of constipation, the use of a laxative will be recommended. If severe constipation is suspected, patients will be referred urgently to gastroenterology for assessment, and treatment will be discontinued.

Fever
- Risk: During clozapine therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment usually lasting for 2-4 days. This fever is generally benign but infection, myocarditis or NMS needs to be considered. Occasionally, it may be associated with an increase or decrease in the WBC count (28).
- Action within trial to minimize risk: Participants will have their temperature recorded at baseline and be advised that fever can occur as a side-effect of clozapine treatment. Participants will be supplied with a digital thermometer and instructed to measure their temperature twice per day for the first 4 weeks of the study. Participants will be advised to ring the study nurse in the event that they develop a fever (> 38°C).
- Action taken if event occurs: Patients with fever will be assessed to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of NMS will be considered.
Hyperglycaemia and Diabetes Mellitus

- **Risk:** Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients with atypical antipsychotics including clozapine and risperidone. There is an increased prevalence of type II diabetes in psychiatric patients (25, 28). In a 5-year naturalistic study of 82 schizophrenia patients treated with clozapine, 52% developed diabetes at completion.
- **Action to prevent:** Patients with diabetes or elevated HbA1c levels at baseline will be excluded from the trial.
- **Action within trial to minimize risk:** Patients enrolled in the trial will have a HbA1c test at baseline and after 3 and 6 months, and be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, and polyphagia during the course of the trial.
- **Action taken if event occurs:** Treatment will be discontinued if the patient develops hyperglycaemia.

Weight gain

- **Risk:** Patients with schizophrenia gain an average of 2.8 kg after 12 weeks of clozapine treatment (average daily doses of 300-400 mg), and significant weight gain has also been reported with risperidone use (23, 25, 30).
- **Action to prevent:** Patients will be advised to refrain from excessive eating in view of the possibility of weight gain.
- **Action within trial to minimize risk:** Weight will be measured at baseline, and monitored at the 3 and 6 month clinical visits.
- **Action taken if event occurs:** The Treating Neurologist may decide to discontinue treatment if the level of weight gain is considered to have a detrimental impact on the patient’s health.

Thromboembolism

- **Risk:** Cases of venous thromboembolism have been reported with antipsychotic medicines. Clozapine and risperidone may cause sedation and weight gain, thereby increasing the risk of thromboembolism (25, 28).
- **Action to prevent:** All patients enrolled in the study will have EDSS of 6.0 or less, meaning they are ambulatory with or without aid for at least 100 metres.
- **Action within trial to minimize risk:** Patients will be encouraged to remain active and mobile.
- **Action taken if event occurs:** Treatment will be discontinued if a participant develops a thromboembolism.

Cerebrovascular

- **Risk:** An increased risk of cerebrovascular adverse events such as stroke and transient ischaemic attacks has been seen in the elderly dementia population with some atypical antipsychotics, including risperidone (25).
- **Action to minimize risk:** Patients over the age of 70 and/or having significant risk factors for cerebrovascular disease will be excluded from the trial.
- **Action taken if event occurs:** Treatment will be discontinued if a participant develops any cerebrovascular adverse events.

Seizures

- **Risk:** There is an increased risk of seizures in patients treated with clozapine, with a 10% cumulative risk over 3.8 years. The risk of seizures relates to the dose and speed of up
titration. Patients on < 300 mg of clozapine per day have a risk of 1% (31). Risperidone use is also associated with an increased risk of seizures, but at a lower level than other atypical antipsychotics (25).

- **Action to minimize risk:** Patients with a history of seizures will be excluded from the study. Clozapine will be slowly up titrated over the first two weeks and the maximum dose held at 150 mg per day. Patients will be cautioned about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others (e.g., driving an automobile, operating complex machinery, swimming, climbing).

- **Action taken if event occurs:** Treatment will be discontinued if a participant develops any seizure activity.

**Tardive Dyskinesia**

- **Risk:** Medicines with dopamine receptor antagonistic properties, including risperidone, have been associated with the induction of tardive dyskinesia (25). Tardive dyskinesia is not thought to be associated with the use of clozapine.

- **Action within trial to minimize risk:** Patients will be assessed for signs and symptoms of tardive dyskinesia during weekly monitoring visits during the first 18 weeks of the trial, and 4 weekly thereafter.

- **Action taken if event occurs:** Discontinuation of treatment should be considered if symptoms of tardive dyskinesia occur.

**Neuroleptic Malignant Syndrome**

- **Risk:** Many antipsychotic drugs, including clozapine and risperidone, have been associated with NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated creatine phosphokinase levels (25, 28).

- **Action within trial to minimize risk:** Patients will be asked to report any symptoms of NMS such as fever or muscle rigidity and in the event that these occur will be advised to seek urgent medical attention. Patients will be supplied with a thermometer for daily temperature monitoring.

- **Action taken if event occurs:** In the event of NMS, treatment will be discontinued.

**Dysphagia**

- **Risk:** Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. Patients with advanced Alzheimer’s dementia have a higher risk of aspiration pneumonia, which can cause morbidity and mortality (25).

- **Action to prevent:** Patients over the age of 70 and/or those with Alzheimer’s dementia or existing dysphagia will be excluded from the trial.

**Hyperprolactinaemia**

- **Risk:** Risperidone can cause rapid, dose-dependent elevations in prolactin that may be sustained. Hyperprolactinaemia can result in hypogonadism, and contribute to a reduction in bone mineral density in pre-menopausal women. There is evidence from in vitro and animal studies that hyperprolactinaemia may increase the risk of breast cancer; however, there is not currently any human data supporting such an association with the administration of antipsychotics (25, 32).

- **Action to prevent:** Patients with pre-existing hyperprolactinaemia will be excluded from the trial, as will those with risk factors for osteoporosis such as age (>70 years), alcoholism, use of glucocorticoids, or hyperthyroidism.

- **Action within trial to minimize risk:** Prolactin levels will be measured at the screening visit, and during the 3 and 6 month clinical visits, and patients will be asked about...
symptoms of hyperprolactinaemia during their regular monitoring consultations with the Research Nurse.

- Action taken if event occurs: In the event of symptomatic hyperprolactinaemia, aetiologies other than the study medicine will be considered. In the absence of an alternative cause for the hyperprolactinaemia, treatment will be discontinued.

**Liver disease**

- Risk: Asymptomatic elevation in transaminases occurs in 30-50% of patients taking clozapine. Icteric hepatitis is uncommon, with a risk of 0.06%.
- Action to prevent: Patients with pre-existing liver disease will be excluded from the study.
- Action within trial to minimize risk: Liver function tests will be assessed at baseline and at 3 and 6 months.
- Action taken if event occurs: If significant elevation of transaminase levels occurs in conjunction with nausea, weakness, and/or abdominal discomfort, treatment will be discontinued.

**Pregnancy**

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the foetus due to clozapine; however, neonates exposed to antipsychotic medicines during the third trimester of pregnancy are at risk of experiencing neurological disturbances and/or withdrawal symptoms following delivery. The safe use of clozapine and risperidone in pregnant women has not been established (25, 28). Women of childbearing age will be advised to use contraception and not to become pregnant during the course of the trial. If a participant does become pregnant while taking a study medicine, they will be withdrawn from the trial.

**Lactation**

Animal studies suggest that clozapine and risperidone are excreted in breast milk (25, 28). Women wishing to breast feed will be excluded from this trial.

**Effects on ability to drive and use machines**

Owing to the ability of clozapine to cause sedation, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment. Similarly, risperidone may interfere with activities requiring mental alertness, therefore patients will be advised not to drive or operate machinery until their individual susceptibility is known.

**Trial Safety Review**

There is limited information regarding the use of clozapine and risperidone in treatment-naïve healthy volunteers, and no previous reports of the use of these medications in patients with PMS. Further, the information that is available concerns using the medications at substantially higher doses. The incidence and extent of the side effects of clozapine and risperidone in the specific patient population being examined in the present study is therefore unclear, and the study protocol has been designed to minimise the likelihood of such events by using a conservative approach to both initiating and monitoring the treatment.

After completion of titration onto the study medication for the first randomization block (n = 3 for each drug), study recruitment will be briefly suspended. Once the first 9 patients have completed their first month in the study (two weeks of up-titration onto the medication and two weeks at the maintenance dose) a study review will be performed by the Treating Neurologist. The primary purpose of this review will be to evaluate the period of monitoring...
required for patients during the initial titration onto the medications, but the review will also examine the rates of AE and study drop-out between the three treatment groups.

If the Treating Neurologist deems a more substantial period of monitoring necessary or there is a high rate of AE or patients declining to continue with treatment, the suitability of continuing with the study will be considered. The criteria for stopping the trial are: 1) an SAE that results in death, significant or persistent disability, or is life threatening or 2) if more than 30% experience persistent intolerable AE leading them to stop the study medication. If a decision is made to continue the study with an increased level of monitoring, the study protocol will be amended and recruitment continued. If it is felt that the period of monitoring should be reduced, a study amendment will be submitted to the Health and Disability Ethics Committees for approval before the study continues recruitment.

**PATIENT COMPENSATION**

It is expected that study participants will encounter transportation costs and devote a significant amount of time in order to make the numerous visits to Wellington Hospital and Southern Community Laboratories sites that are required as part of study participation. For these reasons, study participants will be compensated for their time and expenses; for example with $20 petrol or food vouchers per routine study-related visit, including the screening and clinical visits, dose-monitoring visits, and weekly monitoring appointments at Wellington Hospital. The compensation will be supplied by the Research Nurse at the completion of each study visit, and participants will be asked to sign a register to acknowledge receiving the vouchers.

**DATA MANAGEMENT**

**Case report forms**

Paper CRFs will be used for this study; the EDSS, FSS, and MSFC assessments will use the standard questionnaires; ECG, echocardiogram, MRI, and laboratory test results will be copied, anonymised and replaced with the participant study numbers. The completed forms will be stored between visits by the Research Nurse.

The electronic study documents will be stored using dropbox file sharing system so that the records can be accessed at any time by the Treating Neurologist or Research Nurse.

**Confidentiality and storage**

Data will be held centrally in locked filing cabinets and password protected electronic files, which will only be accessible to study researchers. Patients will be identified with a depersonalised code, which will be stored separately. The data will be stored for 15 years, and the principal investigator will have responsibility for this data.

**MANAGEMENT OF STUDY MEDICATIONS**

**Medicine checking and storage**

The Research Nurse will be responsible for checking the study medicines on arrival, issuing the medicines to study subjects, tracking the stock levels, and monitoring the medicine storage conditions.
Supply of study medicines to participants
The participants will be supplied the study medicine in four separate lots that will be sufficient to cover the intervening gaps (lasting between 4 and 9 weeks). The first supply will be given during the first dose-monitoring visit, and subsequent supplies will be issued during study weeks 9, 13, and 22, during the corresponding clinical or monitoring visits.

Protocol for administering suspension
When a bottle of medicine in suspension form is used, the bottle should be shaken for 10 seconds followed by immediate dispensing of the required dose using an oral dispenser.

Disposal of used and unused study treatments
In the event that a study patient does not complete the full course of treatment, it will be requested that the remaining medicine is returned to the Research Nurse for disposal. At the completion of the trial any unused study treatments will be destroyed according to local guidelines.

STATISTICS

Sample size
A sample size of 12 per treatment group is proposed to allow comparison of the acceptability and safety of clozapine and risperidone treatment to placebo and to provide preliminary data on potential effects on disease parameters (i.e. MSFC, EDSS). The sample size has been calculated based upon the validation of the TSQM-9 by Bharmal et al (20). This study demonstrated that medium compliers had a significantly higher TSQM-9 score than low compliers, and compliance was assessed by the Modified Morisky scale, which evaluates self-reported patient adherence (20). Based upon this data, if we assume a similar effect size as that shown between medium to low compliers (81.25±15.19 compared to 69.82±19.82 for global satisfaction) occurs between either drug treatment compared to placebo over the 6-month treatment, then 11 patients will give us an 80% power of observing a statistically significant result. Thus, a group size of 12 would slightly overpower the study.

While the main comparison is between drug-treatment (clozapine or risperidone) and placebo, if clozapine or risperidone is found to be superior in terms of acceptability and safety and to show efficacy on disease parameters, a phase 2 randomized, placebo-controlled trial can be run to evaluate the efficacy of this superior drug at reducing disease parameters.

Data analysis
Analysis of the trial data will be performed under the guidance of a statistical consultant as follows. The proportion of patients with SAE and AE in each group will be compared (clozapine vs risperidone) by Fisher’s exact test. TSQM-9, change in EDSS, change in FSS, and change in MSFC will be analyzed by Wilcoxon signed-rank test for paired participant analyses. To compare TSQM-9 between placebo, clozapine, and risperidone treatment, a Kruskal-Wallis test (non-parametric; multiple comparison correction) will be used.

PROJECT TIMELINE
Each participant will be involved in the study for a total of 32 weeks, as outlined in the schedule presented in Appendix 1. It is anticipated that the patients will be bulk recruited.
with three per fortnight, taking approximately 24 months to complete. A further 6 months will be required for data analysis, bringing the total study duration to approximately 2.5 years.

**FUTURE RESEARCH**
At present, the mechanism through which clozapine and risperidone reduce disease severity in animal models is not known; therefore, the effect of these medications on the immune system is of interest. During the study, blood samples collected at baseline and the 3 and 6-month clinical visits will be transported to Victoria University for analysis. These samples will be kept for up to five years following completion of the study and will be used for the purpose of investigating the impact of clozapine and risperidone on the human immune system. At the end of the storage period, the samples will be disposed of in accordance with usual practices for biological waste.

**MEDICAL PRINCIPAL INVESTIGATOR AGREEMENT**
By signing this Protocol, the Medical PI acknowledges and agrees to conduct this study as detailed herein, in compliance with The World Medical Association Declaration of Helsinki and the applicable New Zealand ethical and regulatory requirements.

____________________________________ (signature) ___________________ (date)

Dr David Abernethy
REFERENCES

1. 2012. Adult Clozapine Titration Chart.
(TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes* 7: 36


APPENDIX 1: SCHEDULE OF VISITS FOR TRIAL PARTICIPANTS

<table>
<thead>
<tr>
<th>Week 0: Screening Visit</th>
<th>Week 1: Dose Monitoring</th>
<th>Weeks 2-12</th>
<th>Week 13: 3 Month Visit</th>
<th>Weeks 14-18</th>
<th>Weeks 19-25</th>
<th>Week 26: 6 month Visit</th>
<th>Week 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>MRI (Day 1)</td>
<td>Weekly FBC &amp; consult</td>
<td>Clinical assessment</td>
<td>Weekly FBC &amp; consult</td>
<td>4-weekly FBC &amp; consult</td>
<td>Clinical assessment</td>
<td>Final FBC</td>
</tr>
<tr>
<td>Eligibility assessment</td>
<td>Dose monitoring (5 visits)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo-cardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KEY: Treating Neurologist, Assessing Neurologist, Research Nurse, Specialized Technicians
## APPENDIX 2: Dose-monitoring Protocol

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Week Day</th>
<th>Medicine Dose</th>
<th>Site</th>
<th>Monitoring Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M</td>
<td></td>
<td>Clozapine: 5 mg AM, 0 mg PM Risperidone: 0.5 mg AM, 0 mg PM Placebo</td>
<td>Wgtn Hosp</td>
<td>Baseline standing &amp; sitting BP, HR, &amp; temp measured Medicine administered Standing &amp; sitting BP, HR, &amp; temp measured hourly for 4 hrs RN remains with patient for the duration of the visit</td>
</tr>
<tr>
<td>2 T</td>
<td></td>
<td>Clozapine: 10 mg AM, 0 mg PM Risperidone: 0.5 mg AM, 0 mg PM Placebo</td>
<td>Wgtn Hosp</td>
<td>Baseline BP, HR, &amp; temp measured Medicine administered BP, HR, &amp; temp measured at 2 &amp; 4 hrs RN remains with patient for the duration of the visit</td>
</tr>
<tr>
<td>3 W</td>
<td></td>
<td>Clozapine: 15 mg AM, 0 mg PM Risperidone: 0.5 mg AM, 0 mg PM Placebo</td>
<td>Wgtn Hosp</td>
<td>Baseline BP, HR, &amp; temp measured Medicine administered BP, HR, &amp; temp measured at 2 &amp; 4 hrs RN not required to monitor patient continuously</td>
</tr>
<tr>
<td>4 Th</td>
<td></td>
<td>Clozapine: 20 mg AM, 0 mg PM Risperidone: 0.5 mg AM, 0 mg PM Placebo</td>
<td>Wgtn Hosp</td>
<td>Baseline BP, HR, &amp; temp measured Medicine administered BP, HR, &amp; temp measured at 2 &amp; 4 hrs RN not required to monitor patient continuously</td>
</tr>
<tr>
<td>5 F</td>
<td></td>
<td>Clozapine: 25 mg AM, 10 mg PM Risperidone: 0.5 mg AM, 0.5 mg PM Placebo</td>
<td>Wgtn Hosp</td>
<td>Baseline BP, HR, &amp; temp measured Medicine administered BP, HR, &amp; temp measured at 2 &amp; 4 hrs RN not required to monitor patient continuously RN/TN assess if patient requires second week of monitoring</td>
</tr>
<tr>
<td>6 Sat</td>
<td>Same as previous day</td>
<td></td>
<td>-</td>
<td>No monitoring, emergency contact info supplied</td>
</tr>
<tr>
<td>7 Sun</td>
<td>Same as previous day</td>
<td></td>
<td>-</td>
<td>No monitoring, emergency contact info supplied</td>
</tr>
<tr>
<td>8 M</td>
<td></td>
<td>Clozapine: 25 mg AM, 25 mg PM Risperidone: 0.5 mg AM, 0.5 mg PM Placebo</td>
<td>Home</td>
<td>Temp measured at baseline, 2 &amp; 4 hrs Medicine administered RN contacts patient after dosing</td>
</tr>
<tr>
<td>9 T</td>
<td></td>
<td>Clozapine: 25 mg AM, 25 mg PM Risperidone: 0.5 mg AM, 1 mg PM Placebo</td>
<td>Home</td>
<td>Temp measured at baseline, 2 &amp; 4 hrs Medicine administered RN contacts patient after dosing</td>
</tr>
<tr>
<td>10 W</td>
<td></td>
<td>Clozapine: 25 mg AM, 45 mg PM Risperidone: 0.5 mg AM, 1 mg PM Placebo</td>
<td>Home</td>
<td>Temp measured at baseline, 2 &amp; 4 hrs Medicine administered RN contacts patient after dosing</td>
</tr>
<tr>
<td>11 Th</td>
<td></td>
<td>Clozapine: 25 mg AM, 45 mg PM Risperidone: 0.5 mg AM, 1 mg PM Placebo</td>
<td>Home</td>
<td>Temp measured at baseline, 2 &amp; 4 hrs Medicine administered RN contacts patient after dosing</td>
</tr>
<tr>
<td>12 F</td>
<td></td>
<td>Clozapine: 25 mg AM, 60 mg PM Risperidone: 0.5 mg AM, 1.5 mg PM Placebo</td>
<td>Home</td>
<td>Temp measured at baseline, 2 &amp; 4 hrs Medicine administered RN contacts patient after dosing</td>
</tr>
<tr>
<td>13 Sat</td>
<td>Same as previous day</td>
<td></td>
<td>-</td>
<td>No monitoring, emergency contact info supplied</td>
</tr>
<tr>
<td>14 Sun</td>
<td>Same as previous day</td>
<td></td>
<td>-</td>
<td>No monitoring, emergency contact info supplied</td>
</tr>
<tr>
<td>15 M</td>
<td></td>
<td>Clozapine: 25 mg AM, 75 mg PM Risperidone: 0 mg AM, 2 mg PM Placebo</td>
<td>-</td>
<td>No monitoring, emergency contact info supplied</td>
</tr>
</tbody>
</table>